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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/645,121	08/21/2003	Bertrand L. Chenard	PC8315D(16046ZYXW)	6674

23389 7590 11/10/2004

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/645,121	CHENARD ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *3 and 4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5 and 7-10* is/are rejected.

7)☒ Claim(s) *6 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The traverse of the requirement for restriction is unpersuasive. Applicants have argued that the inventions are not independent. MPEP §802.01 has an extensive discussion of the meaning of "Independent" and "Distinct". It concludes, "The law has long been established that dependent inventions (frequently termed related inventions) ... may be properly divided if they are, in fact, "distinct" inventions, even though dependent." Thus, being distinct alone is sufficient; being a dependent is not itself a bar to restriction.

Applicants point to the title, as evidence that there is a "single generic class of compounds". This is unpersuasive. A title cannot establish anything; a title could be "Compounds". Moreover, a genus can always be drawn (e.g. "chemical compounds"), so the mere presence of a genus does not mean that a requirement for restriction is improper.

Applicants point to the classification. This was presented as a) evidence of burden, since many additional subclasses would need to be searched, and b) evidence of distinctness. The fact that piperidines, pyrrolidines, piperazines, etc are all classified separately is evidence that piperidines, pyrrolidines, piperazines, etc are considered structurally distinct.

Applicants point to the description requirement, that 35 USC 112 requires "disclosure of all aspects" of the invention, but that has no bearing on the requirement for restriction.

Applicants final comments about the fees, about the efficacy of a Terminal Disclaimer, and about the efficacy of the third sentence of 35 USC §121 as a shield against "obviousness-type" double patenting are noted, but these are all arguments against the practice of restriction itself, and cannot be taken into account by the examiner.

Thus, claims 1, 2 and 5-11 are objected to as embracive of non-elected subject matter. Limiting R1 to choice II will resolve the matter.

Thus, the requirement for restriction is made Final. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

The designation of this case as a continuation is objected to. Applicants have changed the definition of M in claim 1. The original claims submitted give for the third choice of M this term: (C_24O). The meaning of this text is unknown, but such text did not appear in the parent.

The abstract is objected to as too vague. Formula 1 needs to be inserted for the Abstract to make sense.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5, 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The third choice for M is: (C_24O). The meaning of this text is unknown. For whichever choice is made to fix it, applicants must show that one of ordinary skill in the art would have known that this choice, and not another, was intended.

2. The optional double bond at the top of the XVII choice is very problematic. If it is not present, then the N at the upper left will have only two bonds, which is impossible. But if it is present, then the M = N and M = C~O will both be impossible because M will have too many bonds. The only solution is to put the double bond in, and make M = C.

3. The provisions for A-G, I-L and Z being N are impossible. Since the rings are aromatized, that would give a nitrogen without a charge but having four bonds. That is impossible. These are tetravalent variables, and while C is tetravalent, an uncharged N is not. The structure as drawn is impossible because it violates the rules of chemical bonding. As stated in *In re Zletz*, 13 USPQ2d 1320, 1322, "An essential purpose of patent examination is to fashion claims that are precise, clear, correct and unambiguous." This formula is not correct.

4. Similarly, G, I, J and K being O, S, or CO are likewise impossible. These are all divalent choices for a tetravalent variable. The same issues arise, except that the problem is even worse. Each of G, I, J and K has four bonds, yet the choices, O, S, and CO are only divalent choices.

5. The XVI ring is impossible. This is drawn as a five membered aromatic ring without a central charge, which is impossible. Aromatic rings with odd numbers of atoms must have a charge, ⊖ for a 5 membered ring, ⊕ for a 7 membered ring. This either adds the 6th electron, or removes the 7th respectively to get to the required 6. If applicants disagree, they are invited to draw an example of such a ring, keeping in mind that a) the ring must have exactly 5 members b) the ring must have alternating single and double bonds so that every position is the same c) a bond extends from L as the bond of attachment and d) the letters must be chosen only from the Markush group as given, i.e. C, N, O, S and CO e) there is no charge present.

6. The C_1 alkenyl at page 80, line 10, page 81, line 5 etc is obviously impossible. Likewise for alkynyl.

7. "Heteroalkyl" is indefinite; there is no such thing. Is it an alkyl substituted by a heterocycle, e.g. pyridyl-methyl? An alkyl interrupted by a heteroatom, such as methoxymethyl? An alkyl substituted by a heteroatom, e.g. chloromethyl? Whatever choice is selected must be supported by the specification.

8. Page 81, line 8 has "alkyl ring", which is a contradiction in terms. Likewise, page 81, line 13. An alkyl group by its very nature is open chain; it cannot be a ring.

9. In addition, the ring would have to be formed from not just the two variables, but also the atom to which the variables are attached.

10. Similarly, when variables such as R6-R7 are combined to form rings, these must be with the atoms to which the variables are attached.

11. Claims 7 and 8 appear to be duplicates. A pill is still a pill regardless of what it is designed to be used for.

12. The term "drug abuse" in claim 9 is of unclear scope. Would it include the use of tobacco? Moderate use of marihuana? The use of steroids in body-building?

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope of the claim is unknown. Which diseases are these? Determining whether a given disease is involved with deficient serotonin neurotransmission will surely involve undue experimentation. The roles played by the major neurotransmitters are quite complex, and understanding is limited. Moreover, the "deficient serotonergic neurotransmission" would cover a whole range of types of problems, including the production of serotonin, where and when it is released, and in what quantity, and its reuptake. Complicating this is the fact that there are more than a dozen molecularly different serotonin receptors. Moreover, there are multiple, discrete neuronal and nonneuronal (including endocrine) pathways and mechanisms that mediate the many functions of serotonin, which includes its role as a neuromodulator. The full range of disorders involved with serotonin neurotransmission is simply not known at present, nor could it be determined without undue experimentation. Moreover, there are many mental disorders whose origins are unknown, e.g. autism. Thus, autism may or may not fall into the scope of claim 10; there is no way of knowing whether autism does or does not arise from "deficient serotonergic neurotransmission" because no one has determine what autism arises from. The same is true for e.g. ADHD and mental retardation, and many neurodegenerative disorders, just as some examples. What these arise from is

unknown, so it is unknown whether these arise from some problem in "deficient serotonergic neurotransmission".

Suppose that a given agonist or antagonist X when administered to a patient with Disease D does not obtain an improvement in serotonin neurotransmission. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another agonist or antagonist Y is potent enough, so that D really does fall within the claim. Thus, how many different agonists or antagonists must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Suppose that X really will work, but only when combined with Z. One must then check multiple types of Z.

G. Further, if the compound were active both at $5HT_1$ and some other 5 HT receptor, it would be a significant task to determine whether the $5HT_1$ at all contributed to the actual effect.

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The compounds are disclosed to be active at 5HT1. However, serotonin is regulated at many receptors. In addition to the five 5HT1 receptors, there are three 5-HT2 (5-HT2A/2B/2C), two 5HT3 (5-HT3A/3B) two 5HT4 (5-HT4A/4B) two 5HT5 (5-HT5A/5B), 5HT6 and four 5HT7 receptors (5-HT7A/7B/7C/7D). Diseases that are regulated by these but not the five 5-HT1 receptors would not be expected to be affected by these compounds, since these compounds are not disclosed to be active at these sites. Yet, such disorders would fall within the ambit of claim 10.

Claims 9-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims cannot be considered enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Primarily because of the deeply nested nature of R2, the claim covers billions of compounds. R2 can be many choices, nearly all of which terminate in R4. R4 can be hundreds of different types of monocyclic, bicyclic, tricyclic and even tetracyclic ring systems, each substituted, sometimes with as many as 5 substituents, and these substituents have many, many choices, most of which can be substituted with still more substituents.

(b) Scope of the diseases covered. As noted above, the scope of claim 10 is unknown. Claim 9 has an assortment of conditions. Most are individual disorders, such

as migraine and Alzheimer's Disease. However, two are categories. There is eating disorders, which embraces obesity (general over-eating), pica, anorexia, bulimia, binge-eating, and other compulsive eating disorders. The second category is "drug abuse". This covers the use of a very broad range of quite different drugs, including illicit drugs (e.g. illegal stimulants, hallucinogens, depressants, etc), legal drugs (alcohol and possibly nicotine), inhalants (e.g. glue sniffing) and abuse of legal pharmaceuticals such as OxyContin. As noted in point 12 above, its scope is unclear.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The smallest dosage range given is 300-fold (page 27, lines 15-17). Moreover, this is generic, the same for the many very different disorders covered by the specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for these claimed disorders. The specification teaches that the compounds are agonists and antagonists of the $5HT_1$ receptor. Of course, a given compound cannot have both properties. More seriously, the specification does not say which $5HT_1$ receptor these compounds are active at.

(4) State of the Prior Art: These compounds are piperazine compounds attached to a naphthylene ring with a particular substitution pattern. So far as the examiner is aware, no naphthyl-piperazines of any kind have been used for the treatment of such disorders.

(5) Working Examples: There are none for any disorder, or for any model of any disorder. In fact, the specification presents no specific biological data of any kind for any specific compound.

(6) Skill of those in the art: The art recognizes that there really isn't a $5HT_1$ receptor per se, but rather that there are $5HT_1A$, $5HT_1B$, $5HT_1D$, $5HT_1E$, and $5HT_1F$, and others may be discovered as well. It is unknown from the specification which one(s) these are supposed to be effective against. This is an important consideration, because these different receptor subtypes mediate different biological processes. 5-HT1A receptor activation hyperpolarizes and inhibits CA3 pyramidal neurons in the dorsal hippocampus, and stimulates neurite branching, lowers body temperature, stimulates appetite, relieves anxiety, stimulates sexual behavior. 5-HT1B is involved the modulation of aggression, the response to cocaine, and locomotor hyperactivity, and vasoconstriction of cranial arteries, and inhibits appetite. Very little is known about $5HT_1E$, and $5HT_1F$, and essentially nothing at all as of 2/1994. Compounds in this area tend to have a complex profile because of a mixture of activities. For example, Sumatriptan is a potent and selective agonist at the vascular $5HT_1D$ receptor, and at the 5-HT1B receptor, and is effective for treating migraine and cluster headaches, so that if these compounds are $5HT_1D/B$ agonists, such a utility would be enabled. On the other

hands, such $5HT_1D$ receptor agonists (such as Sumatriptan) constrict human coronary arteries, and thus would be expected to make hypertension actually worse, not better. Ziprasidone is a serotonin 1D antagonist, but a serotonin 1A agonist. On the other hand, Urapidil is an antihypertensive agent with dual action (alpha 1-adrenergic antagonist and $5HT_1A$ agonist) and is well established in the treatment of arterial hypertension. Thus, if the compounds here were $5HT_1A$ agonists, hypertension would be the utility enabled, not the others. The $5HT_1A$ agonist Buspirone has also been shown effective for treatment of some types of pain. Moreover, this represents what is known at present. Knowledge as of the filing date of 2/1994 was much more limited. The specification provides no guidance in such matters, and it appears that such considerations were not even known at the time. The use of the plural does not mean that there is disclosure of more than one type of $5HT_1$ receptor being referred to. The plural simply refers to the fact that there are many copies of any given type in the body. Thus, if one were to say that a compound agonized the $5HT_1A$ receptors in the body, it would be understood as saying that the numerous $5HT_1A$ receptors in the body were agonized, not that there were different types of $5HT_1A$ receptors in the body, all types of which were agonized. The specification, as written, is simply silent on the subject of which type of $5HT_1$ receptor is being referred to. If applicants actually believe, as was apparently argued in the grandparent application, that the specification would be understood by one of ordinary skill in the art as saying that the compounds are active against all of $5HT_1A$, $5HT_1B$, $5HT_1D$, $5HT_1E$, and $5HT_1F$, applicants are invited to present a declaration to that effect.

Drug abuse is listed. The notion that a compound could be effective against chemical dependencies in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "drug abuse" generally. That is because "drug abuse" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc. all involve different parts of the CNS system; different receptors in the body. Many do not appear to involve serotonin at all. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction arises from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find a pharmaceutical to treat drug abuse generally have thus failed. Indeed, the examiner is unaware of any form of drug abuse for which those skilled in the art had as of 2/1994 found a method of using any of the $5HT_1A$, $5HT_1B$, $5HT_1D$, $5HT_1E$, and $5HT_1F$ agonists or antagonists.

With regard to eating disorders, Fluoxetine regulates appetite. $5HT_1A$ receptors regulate synaptic levels of serotonin. A combination of a $5HT_1A$ receptor antagonist and Fluoxetine might enhance extracellular levels of serotonin over what is obtained with Fluoxetine alone. Thus, a combination of Fluoxetine and a $5HT_1A$ antagonist might be found to be able to enhance the ability of Fluoxetine's appetite suppression. However, that is not the same thing as using such an antagonist alone for this purpose, which is what the claim has.

Chronic paroxysmal hemicrania (CPH) is a poorly understood disorder of unknown origins. Serotonin receptor agonists which are effective against cluster headaches and migraine, e.g. Sumatriptan are ineffective against CPH, which is evidence that these compounds would not be expected to work, and indeed that serotonin might not be involved at all in this disorder.

Claim 9 also lists pain. To treat pain in general, one must use an analgesic. There is no reason to think that serotonin agonists can do this, because none has accomplished this. The fact that a drug can ease the pain of headache does not mean that it can treat pain generally, since headache pain is a very specialized form, unrelated to the more common forms of pain that come from physical trauma, cancer, etc.

The skill level for Alzheimer's Disease is considered low. Alzheimer's Disease is an extraordinarily difficult disease to treat, and has been the subject of a vast amount of research. Despite an enormous number of different approaches, the skill level in the art is so low relative to the difficulty of task that the only success has come from treatment by compounds which are Acetylcholinesterase inhibitors (Aricept®, Cognex®, Exelon®, and Reminyl®), or voltage-dependent NMDA-antagonists (Memantine), properties these compounds are not disclosed to have. Indeed, serotonin is not currently even considered an important research area.

(7) The quantity of experimentation needed: In view of the above factors, especially 1, 3, 5 and 6, the amount needed is expected to be substantial.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571)272-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at 571-272-0661. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

Mark L. Berch
Primary Examiner
Art Unit 1624

November 3, 2004